

# Effects of *Caralluma russeliana* stem extract on some physiological parameters in streptozotocin-induced diabetic male rats

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**Purpose:** The aim of this study was to investigate the effects of *Caralluma russeliana* stem extract on some physiological parameters in streptozotocin induced diabetes in male Wistar rats after 8 weeks.

**Materials and methods:** The experimental rats were randomly assigned into four groups. Rats of group 1 were normal controls. Rats of group 2 were diabetic controls. Rats of group 3 were diabetic rats treated with *C. russeliana* stem extract. Rats of group 4 were non-diabetic rats, subjected to *C. russeliana* stem extract.

**Results:** The lowest body weight gain was noticed in diabetic rats of group 2. Serum glucose, triglycerides, cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, alanine aminotransferase, aspartate aminotransferase, ALP, total bilirubin, creatinine, blood urea nitrogen (BUN) and uric acid levels were significantly elevated in diabetic rats of group 2; however, total serum protein, albumin and high-density lipoprotein cholesterol were significantly reduced in diabetic rats of group 2.

**Conclusion:** Treatments with *C. russeliana* stem extract in diabetic rats revealed notable diminishing and protecting effects of physiological modifications. Therefore, this study revealed the significance of using *C. russeliana* stem extract as a promising remedial agent to treat diabetes and its complications.

**Keywords:** *Caralluma russeliana*, diabetes, streptozotocin, weight loss, glucose, lipids, liver enzymes, kidney function, rats

## Introduction

Diabetes mellitus (DM) is a chronic metabolic syndrome characterized by elevated blood glucose levels with disturbance of carbohydrate, lipid and protein metabolism due to the insufficient insulin secretion, inadequate insulin action, or a combination of both.<sup>1</sup> DM is a disorder influencing 366 million persons worldwide, a number that might increase to 552 million by 2030.<sup>2</sup> The complications of DM are classified as microvascular (retinopathy, neuropathy and nephropathy) or macrovascular (cardiovascular and cerebrovascular diseases).<sup>3</sup> Glycemic control in type 2 DM is currently complex despite the availability of many pharmacological agents and growing concerns about their potential adverse effects.<sup>4-7</sup> Furthermore, elevated glycemic management is hard to accomplish, and previous studies have revealed numerous causes contributing to inadequate management among diabetic persons.<sup>8-10</sup> The International Diabetes Federation has verified that Saudi Arabia is one of the top 10 countries with the maximum DM rates in adults worldwide.<sup>11</sup> In addition, the incidence in Saudi Arabia

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has increased speedily in recent years.<sup>12</sup> Diabetes may be induced by particular destruction of  $\beta$ -cells of the pancreas with a single, fast injection of streptozotocin (STZ). STZ has been utilized as a diabetogenic agent in animals.<sup>13–17</sup> There is currently no adequate efficient treatment to heal diabetes. DM control by insulin has a number of problems such as insulin resistance.<sup>18</sup> Furthermore, in chronic administration, it causes fatty liver, anorexia nervosa and brain atrophy.<sup>19</sup>

Medicinal herbs and plants have commonly been a significant tool for discovering new therapies to cure human diseases. Diverse herbs have traditionally been used for diabetes management. Many investigators have documented the antidiabetic properties of several plants.<sup>20</sup> The plants of genus *Caralluma* are generally distributed in Africa, Asia, Southeast Europe, Canary Islands, Arabian Peninsula and South Africa.<sup>21,22</sup> The species of genus *Caralluma* (family Apocynaceae) are xerophytic plants. Formerly, genus *Caralluma* is a member of family Asclepiadaceae.<sup>23</sup> *Caralluma* species are small, erect and fleshy plants. They are mostly succulent perennial herbs, some of which are documented as edible species.<sup>24</sup> Different medicinal utilizations of *Caralluma* species have been reported in the Indian and Arabic traditional medicine such as in the therapy of cancer, diabetes, inflammation, tuberculosis, skin rashes, scabies, fever, snake and scorpion bites.<sup>25–28</sup> Most general utilizations of these plants have been documented as a famine food without any negative effect recorded. In general, species of *Caralluma* contain several components such as pregnane glycosides, flavone and megastigmane glycosides and different esters, which confirm their medicinal value.<sup>29–31</sup> Antidiabetic, anticancer, antioxidant, anti-inflammatory, antieczemic, antimicrobial and antifungal characteristics of the different extracts of *Caralluma* demonstrated their pharmacological significance.<sup>31,32</sup>

In this study, *Caralluma russeliana* was collected from the outskirts of Taif city in Saudi Arabia during 2015. There is little research about the antidiabetic activities of this species. Therefore, we hoped 1) to distinguish antidiabetic properties of this species and 2) to demonstrate a relationship between its traditional uses and scientific research, postulating that the tested physiological parameters, for the first time, would improve in diabetic animals after administration of *C. russeliana* stem extract. Several species of *Caralluma* contain a number of bioactive components, which confirm their medicinal value and their pharmacological significance. They possess antidiabetic, anticancer, antioxidant, anti-inflammatory and antimicrobial characteristics. In addition, a number of *Caralluma* species have been reported in the traditional medicine for the treatment of various diseases

such as diabetes, cancer, inflammation, tuberculosis, skin rashes, scabies and fever.<sup>25–32</sup> Thus, the aims of this study are to examine the effects of *C. russeliana* stem extract on certain physiological parameters in male Wistar rats with STZ-induced diabetes after 8 weeks and to prove a relationship between the traditional utilizations and scientific research.

## Materials and methods

### Animals

Eighty adult male Wistar rats (180.1–219.5 g) were used in this study. The rats were obtained from the Animal Unit of King Fahd Medical Research Center, King Abdulaziz University, Jeddah. Animals were acclimated to the laboratory circumstances for 1 week before the start of the experiments. All rats were kept in standard plastic cages and sustained under controlled laboratory situations of humidity (55%±10%), temperature (24°C±1°C) and light (12/12-hour light/dark cycle). They were fed *ad libitum* on normal commercial pellet diet and had free access to water. All experiments were performed according to ethical guidelines of the animal care and use committee of King Abdulaziz University, Saudi Arabia. The research was approved by the committee of King Abdulaziz University, Jeddah, Saudi Arabia.

### Extraction of *C. russeliana* stems

Fresh *C. russeliana* stems were collected from Taif city outskirts in Saudi Arabia during July 2015. The plant was scientifically defined by the herbarium of the Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah. A voucher specimen (No 9721) has been deposited in the herbarium of Department of Biological Sciences, Faculty of Science, King Abdulaziz University. The collected samples were totally washed and then dried at room temperature and stored in dry containers until extraction. The method of Al-Attar and Abu Zeid<sup>33</sup> was used to prepare the extract of *C. russeliana* stem with some alterations. The aqueous extracts were prepared every 2 weeks. The dried samples of *C. russeliana* (150 g) were powdered and then added to 6 L of hot water. After 5 hours, the mixture was gradually boiled for 1 hour. After that, the mixture was cooled at room temperature, and it was coarsely blended in an electric mixer for 20 minutes. Then, plant solutions were filtered using 250 mm filter papers (Whatman, Maidstone, UK). The filtrates were finally evaporated in an oven at 40°C to make dried residues (active principles). With regard to the powdered samples, the yield mean of *C. russeliana* stem extract was 20.2%. Afterward, this extract was stored in a refrigerator for the following experiments.

## Diabetes induction

DM was induced in rats by intraperitoneal (i.p.) injection of STZ (Sigma-Aldrich Co., St Louis, MO, USA) at a single dose of 60 mg/kg body weight dissolved in saline solution after overnight fasting. Afterward, STZ-injected animals had free access to water and food. Diabetes was permitted to develop and become stable in these STZ-treated animals over 4 days. They were considered diabetic rats if their fasting blood glucose levels were over 300 mg/dL.

## Study design

The experimental animals were randomly assigned into four groups, each group consisting of 20 rats. The groups were treated as follows:

1. Rats of group 1 were the normal control.
2. Diabetic rats of group 2 were the diabetic control.
3. Diabetic rats of group 3 were orally supplemented with *C. russeliana* stem extract at a dose of 300 mg/kg body weight/day.
4. Non-diabetic rats of group 4 were orally supplemented with *C. russeliana* stem extract at a dose of 300 mg/kg body weight/day.

In this study, the extract dose (300 mg/kg body weight/day) refers to the weight of the concentrated plant extract. All experimental treatments continued for 8 weeks.

## Weight determinations

The weights of rats were determined at the beginning of the experimental period and after 8 weeks using a digital balance. The experimental rats were also noted for abnormality signs during the study.

## Blood serum analyses

After 8 weeks, rats were fasted for 8 hours; water was unrestricted, and then blood samples were collected from the orbital venous plexus of diethyl ether anaesthetized rats into non-heparinized tubes. Then, blood specimens were centrifuged at 2,500 rpm for 15 minutes, and the clear samples of

blood serum were separated and stored at  $-80^{\circ}\text{C}$ . The serum samples were utilized to measure the levels of glucose, total protein, albumin, triglycerides, cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), ALP, total bilirubin, creatinine, blood urea nitrogen (BUN) and uric acid. All these parameters were determined using an automatic analyzer (Architect c8000 Clinical Chemistry System, Abbott, IL, USA).

## Statistical analyses

Data were analyzed using SPSS Package for windows, version 13.0 (IBM Corporation, Armonk, NY, USA). Results were presented as mean  $\pm$  standard error of the mean (SE). Comparisons among groups were carried out using one-way ANOVA, followed by a least-significant difference (LSD) test.  $P < 0.05$  was considered to be significant.

## Results

Body weights of all experimental groups after 8 weeks are shown in Table 1 and Figure 1. The maximum weight gain was noted in normal control rats (+59.2%) after 8 weeks. A significant decrease (−17.9%) in weight gain was noticed in diabetic rats fed on normal diet. Weight gain change was +22.8% in diabetic rats supplemented with *C. russeliana* extract. The percentage change in weight gain in rats treated with *C. russeliana* extract was +31.6%. Compared to group 1, there were significant decreases in weight of group 2 ( $P < 0.0001$ ), group 3 ( $P < 0.0001$ ) and group 4 ( $P < 0.0001$ ).

The measured levels of serum glucose in control (group 1), STZ (group 2), STZ plus *C. russeliana* extract (group 3) and *C. russeliana* extract (group 4)-treated rats are given in Table 2 and Figure 2A. A significant rise in the level of serum glucose was noted in diabetic rats of group 2 (+369.2%,  $P < 0.0001$ ) compared to normal control rats of group 1. Insignificant alterations were observed in serum glucose levels in diabetic (group 3) and non-diabetic (group 4)

**Table 1** Effects of *Caralluma russeliana* stem extract on body weight in STZ-diabetic and non-diabetic rats (n=20)

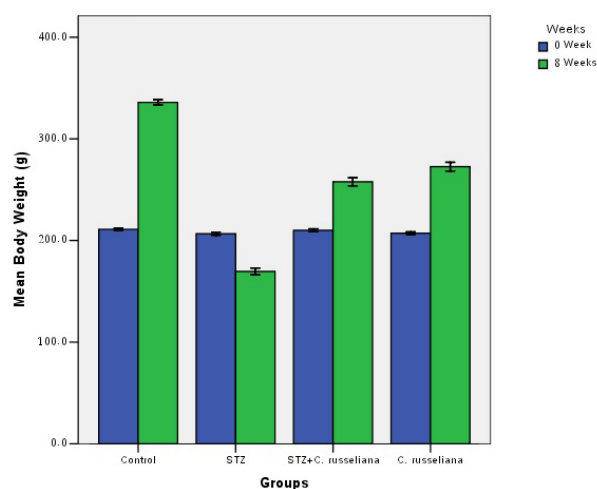
Groups	Body weight (g) (0 week)	Body weight (g) (8 weeks)	Percentage change in body weight
Control	211.0 $\pm$ 0.9	335.9 $\pm$ 2.7	+59.2
STZ	206.7 $\pm$ 1.5	169.6 $\pm$ 3.4 <sup>a</sup>	−17.9 <sup>a</sup>
STZ+ <i>C. russeliana</i>	210.0 $\pm$ 1.5	257.8 $\pm$ 3.9 <sup>a,b</sup>	+22.8 <sup>a,b</sup>
<i>C. russeliana</i>	207.2 $\pm$ 1.3	272.7 $\pm$ 4.3 <sup>a,b</sup>	+31.6 <sup>a,b</sup>

**Notes:** Values are expressed as mean  $\pm$  SE. <sup>a</sup>Significant difference from the normal control group after 8 weeks at  $P < 0.05$ . <sup>b</sup>Significant difference from STZ (the diabetic group) after 8 weeks at  $P < 0.05$ .

**Abbreviations:** SE, standard error; STZ, streptozotocin.

animals treated with *C. russeliana* extract compared to normal control rats (group 1).

Compared to control rats (group 1), a significant decline in the level of serum total protein was observed in diabetic animals of group 2 (−11.9%,  $P=0.007$ ). There were no significant variations in serum total protein levels in rats of STZ plus *C. russeliana* extract (group 3) and *C. russeliana* extract-treated rats (group 4) compared to normal control animals of group 1 (Table 2 and Figure 2B).



**Figure 1** Changes in body weight in control, STZ, STZ plus *Caralluma russeliana* extract and *C. russeliana* extract-treated rats after 8 weeks.

**Notes:** Error bars:  $\pm 1$  standard error of the mean ( $n=20$ ).

**Abbreviation:** STZ, streptozotocin.

There was a significant decrease in serum albumin level in the diabetic rats of group 2 (−15.4%,  $P=0.004$ ). However, there were no significant variations in serum albumin levels in diabetic rats (group 3) and non-diabetic rats (group 4) compared to rats of group 1 (Table 2 and Figure 2C).

There was an increase in serum cholesterol level ( $P<0.0001$ ) in diabetic rats (group 2) compared to other groups. However, serum cholesterol levels were significantly reduced in diabetic rats of group 3 ( $P=0.007$ ) and non-diabetic group 4 ( $P<0.0001$ ) compared to control rats of group 1. Furthermore, serum cholesterol level was significantly declined ( $P<0.0001$ ) in non-diabetic rats of group 4 compared with other groups (Table 2 and Figure 3A).

Compared with control rats (group 1), the level of serum triglycerides was significantly elevated in diabetic rats (group 2) (+100%,  $P<0.0001$ ). Insignificant changes in the levels of serum triglycerides were noticed in rats of groups 3 and 4 compared to normal rats of group 1 (Table 2 and Figure 3B).

Serum HDL-C level was significantly declined in rats of group 2 (−25.8%,  $P=0.01$ ) and group 3 ( $P=0.041$ ) compared to normal control rats of group 1 (Table 2 and Figure 3C).

The level of serum LDL-C was statistically evoked in diabetic rats of group 2 (+121.5,  $P<0.0001$ ) compared with normal control rats of group 1. Insignificant change was noticed in the serum LDL-C level in rats of groups 3 and 4 (Table 2 and Figure 3D).

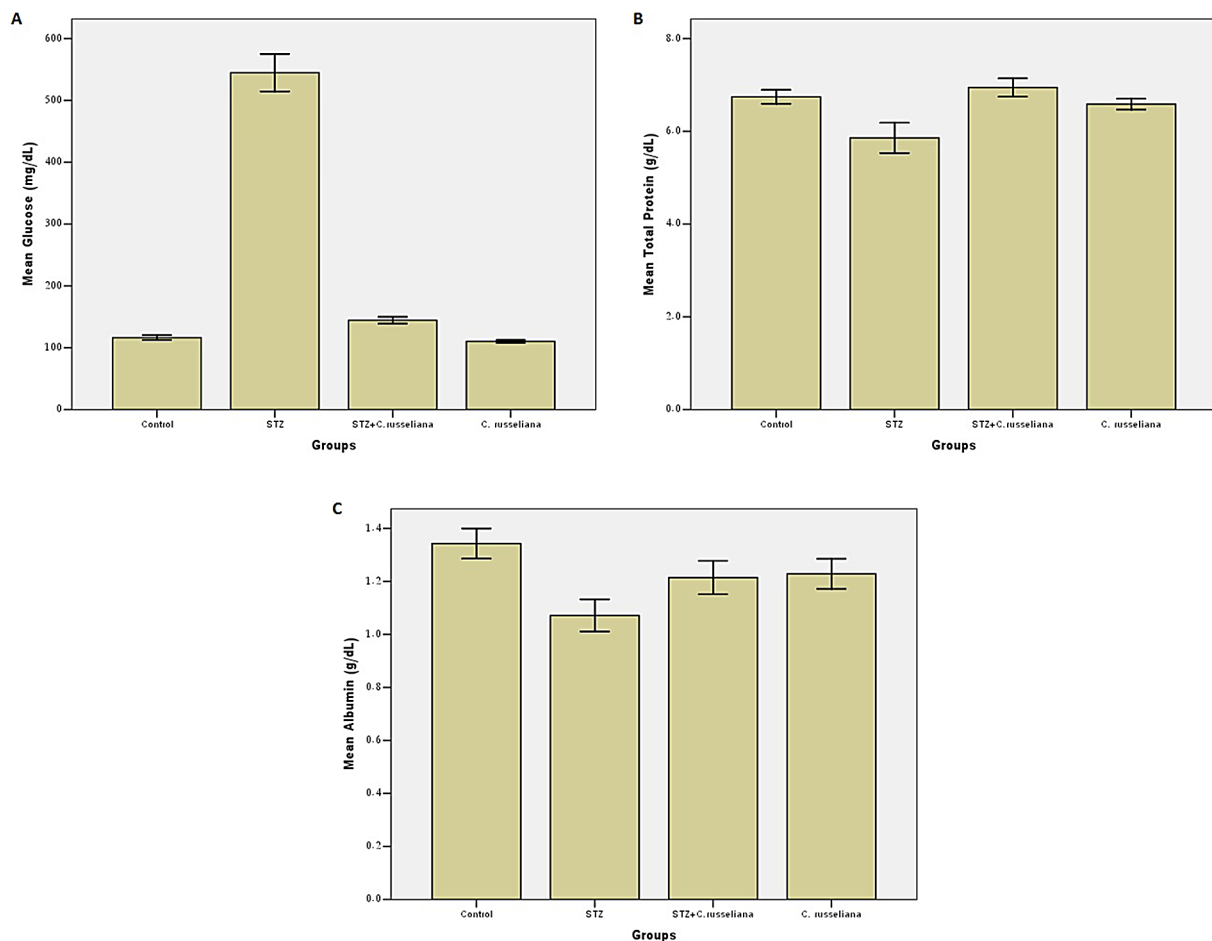
Noticeable increase in serum VLDL-C was observed in diabetic rats (group 2) (+97%,  $P<0.0001$ ) as compared

**Table 2** Effects of *Caralluma russeliana* stem extract on the levels of hematobiochemical parameters in the experimental diabetic and non-diabetic rats ( $n=7$ )

Parameters	Treatments			
	Control	STZ	STZ + <i>C. russeliana</i>	<i>C. russeliana</i>
Glucose (mg/dL)	116.14 $\pm$ 3.96	544.86 $\pm$ 30.27 <sup>a</sup>	144.43 $\pm$ 5.67 <sup>b</sup>	110.14 $\pm$ 2.20 <sup>b</sup>
Total protein (g/dL)	6.74 $\pm$ 0.15	5.86 $\pm$ 0.33 <sup>a</sup>	6.94 $\pm$ 0.20 <sup>b</sup>	6.59 $\pm$ 0.12 <sup>b</sup>
Albumin (g/dL)	1.34 $\pm$ 0.06	1.07 $\pm$ 0.06 <sup>a</sup>	1.21 $\pm$ 0.06	1.23 $\pm$ 0.06
Cholesterol (mg/dL)	64.71 $\pm$ 1.02	75.71 $\pm$ 1.17 <sup>a</sup>	59.29 $\pm$ 1.67 <sup>ab</sup>	42 $\pm$ 1.22 <sup>ab</sup>
Triglycerides (mg/dL)	51.43 $\pm$ 1.94	101.57 $\pm$ 6.81 <sup>a</sup>	55 $\pm$ 4.97 <sup>b</sup>	52.29 $\pm$ 2.97 <sup>b</sup>
HDL-C (mg/dL)	53 $\pm$ 2.98	39.76 $\pm$ 1.81 <sup>a</sup>	42.71 $\pm$ 2.67 <sup>a</sup>	51.43 $\pm$ 5.09 <sup>b</sup>
LDL-C (mg/dL)	7.94 $\pm$ 0.66	17.51 $\pm$ 1.92 <sup>a</sup>	7.69 $\pm$ 1.58 <sup>b</sup>	8.69 $\pm$ 0.91 <sup>b</sup>
VLDL-C (mg/dL)	23.67 $\pm$ 0.89	46.71 $\pm$ 3.12 <sup>a</sup>	25.29 $\pm$ 2.84 <sup>b</sup>	24.07 $\pm$ 1.36 <sup>b</sup>
ALT (U/L)	65.86 $\pm$ 2.46	117.43 $\pm$ 2.87 <sup>a</sup>	64 $\pm$ 3.81 <sup>b</sup>	59.86 $\pm$ 1.63 <sup>b</sup>
AST (U/L)	163.14 $\pm$ 6.26	195.86 $\pm$ 2.18 <sup>a</sup>	159.29 $\pm$ 6.94 <sup>b</sup>	158.71 $\pm$ 4.08 <sup>b</sup>
ALP (U/L)	166.14 $\pm$ 5.63	473.86 $\pm$ 15.54 <sup>a</sup>	203.43 $\pm$ 4.12 <sup>ab</sup>	164.86 $\pm$ 3.66 <sup>b</sup>
Total bilirubin (mg/dL)	0.12 $\pm$ 0.01	0.19 $\pm$ 0.01 <sup>a</sup>	0.12 $\pm$ 0.01 <sup>b</sup>	0.11 $\pm$ 0.01 <sup>b</sup>
Creatinine (mg/dL)	0.47 $\pm$ 0.02	0.65 $\pm$ 0.02 <sup>a</sup>	0.45 $\pm$ 0.02 <sup>b</sup>	0.48 $\pm$ 0.03 <sup>b</sup>
BUN (mg/dL)	52.86 $\pm$ 2.53	131.29 $\pm$ 4.35 <sup>a</sup>	51.86 $\pm$ 5.51 <sup>b</sup>	45.43 $\pm$ 1.63 <sup>b</sup>
Uric acid (mg/dL)	1.28 $\pm$ 0.15	1.94 $\pm$ 0.10 <sup>a</sup>	1.36 $\pm$ 0.09 <sup>b</sup>	1.36 $\pm$ 0.18 <sup>b</sup>

**Notes:** Values are expressed as mean $\pm$ SE. <sup>a</sup>Significant difference from the normal control group at  $P<0.05$ . <sup>b</sup>Significant difference from STZ (the diabetic group) at  $P<0.05$ .

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SE, standard error; STZ, streptozotocin; VLDL-C, very low-density lipoprotein cholesterol.



**Figure 2** Level of serum glucose (A), total protein (B) and albumin (C) in control, STZ, STZ plus *Caralluma russeliana* extract and *C. russeliana* extract-treated rats after 8 weeks. Error bars:  $\pm 1$  standard error of the mean ( $n=7$ ).

**Abbreviation:** STZ, streptozotocin.

to normal control rats (group 1). However, this value was insignificantly altered in rats of groups 3 and 4 compared to normal control rats of group 1 (Table 2 and Figure 3E).

Compared to normal control rats (group 1), statistical increase in the level of serum ALT was noted in diabetic rats of group 2 (+77.3%,  $P<0.0001$ ). Furthermore, the ALT level was statistically unchanged in rats of groups 3 and 4 compared to normal control rats of group 1 (Table 2 and Figure 4A).

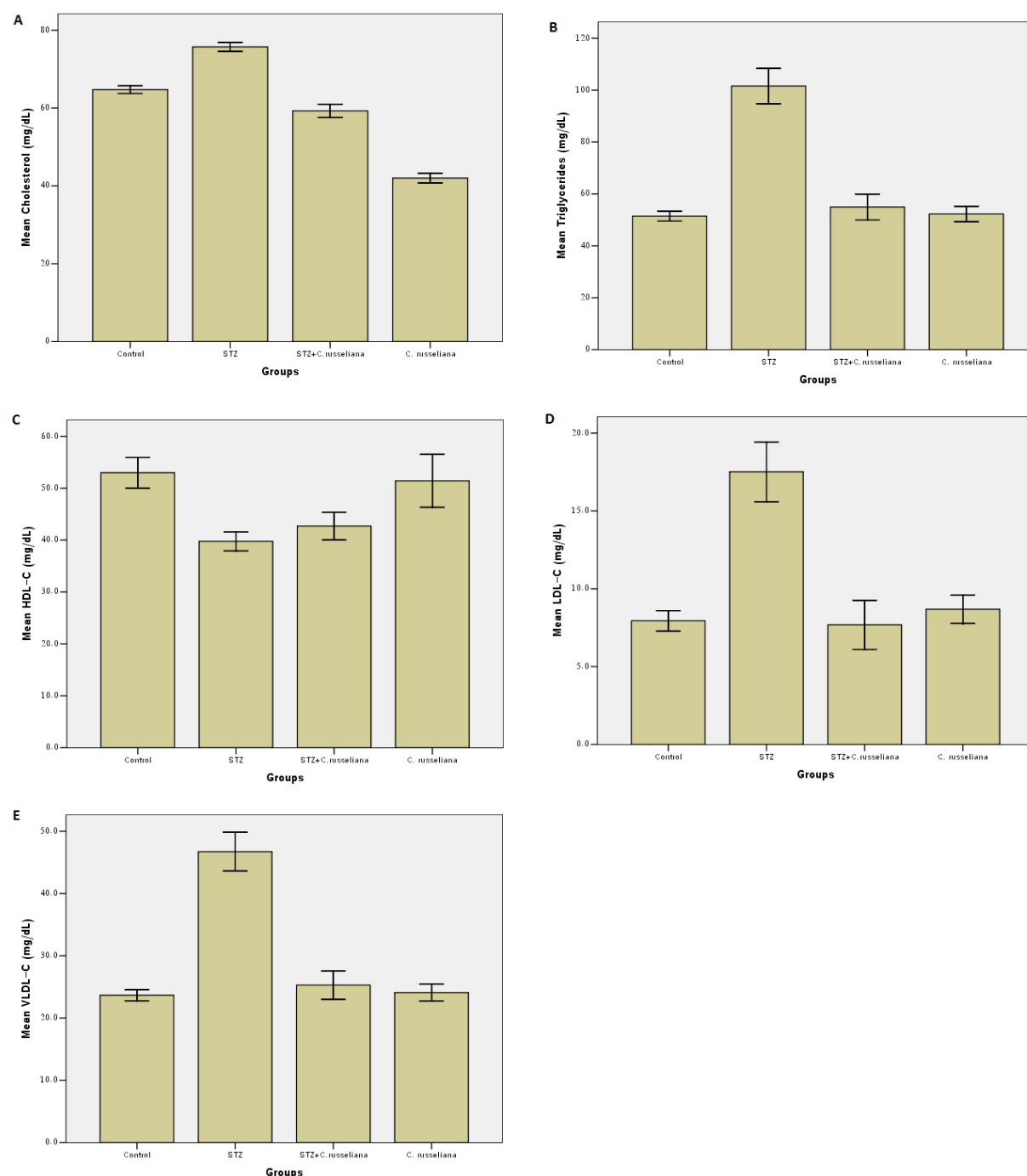
Serum AST level was significantly increased in diabetic rats of group 2 (+20.2%,  $P<0.0001$ ). This value was statistically unaltered in rats of groups 3 and 4 compared to normal control rats of group 1 (Table 2 and Figure 4B).

As shown in Table 2 and Figure 4C, serum ALP levels were significantly elevated in diabetic rats of group 2 (+185.5%  $P<0.0001$ ) and group 3 (+23.5%,  $P=0.006$ ) compared to normal control rats (group 1). However, there was

no significant change in the serum ALP level in non-diabetic rats (group 4) compared to normal control rats (group 1).

Table 2 and Figure 4D show the serum total bilirubin level in all groups. Serum total bilirubin level was statistically evoked in diabetic rats of group 2 (+58.3%,  $P<0.0001$ ) compared to normal control rats (group 1), while there were no significant changes in serum total bilirubin levels in rats of groups 3 and 4. The measured levels of serum creatinine in all groups are shown in Table 2 and Figure 5A. Compared to control rats, serum creatinine level was increased in diabetic rats of group 2 (+38.3%,  $P<0.0001$ ). Insignificant alterations were found in serum creatinine levels in rats of groups 3 and 4.

Serum BUN level was significantly increased in diabetic rats of group 2 (+147.2,  $P<0.0001$ ) compared with control level in normal rats (group 1). Serum BUN levels were remarkably unchanged in rats of groups 3 and 4 (Table 2 and Figure 5B).



**Figure 3** Level of serum cholesterol (A), triglycerides (B), HDL-C (C), LDL-C (D) and VLDL-C (E) in control, STZ, STZ plus *Caralluma russelliana* extract and *C. russelliana* extract-treated rats after 8 weeks. Error bars:  $\pm$ 1 standard error of mean (n=7).

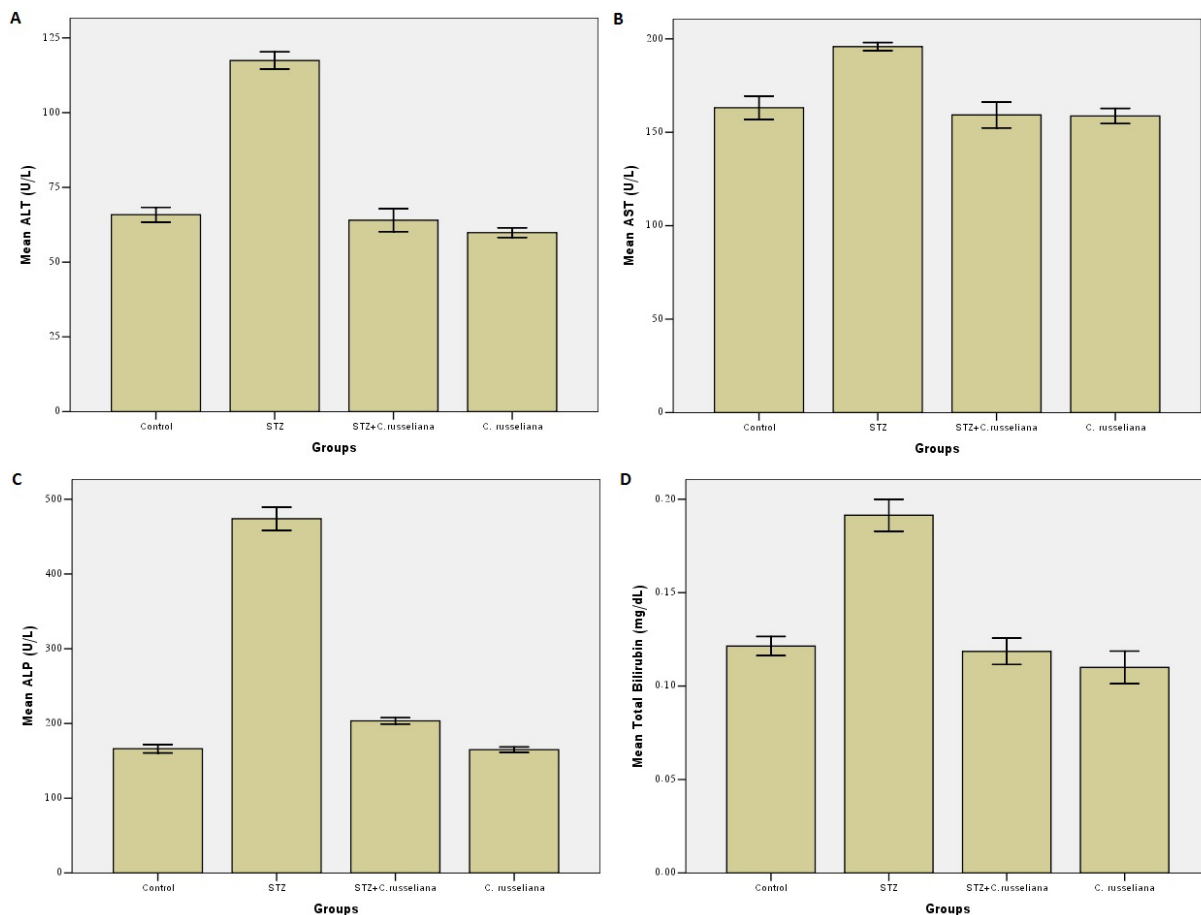
**Abbreviations:** HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; STZ, streptozotocin; VLDL-C, very low-density lipoprotein cholesterol.

Table 2 and Figure 5C represent serum uric acid levels in all groups. Serum uric acid level was statistically enhanced in diabetic rats of group 2 (+46.2%,  $P=0.002$ ) compared to normal control rats (group 1). Insignificant alterations in serum uric acid levels were noticed in diabetic rats of group 3 and non-diabetic rats of group 4 compared to normal control rats (group 1).

## Discussion

DM is a global epidemic syndrome that occurs worldwide. The elevated incidence of DM motivated the investigators to search for antidiabetic agents in the traditional medicine. The use of traditional remedies against DM has yielded good results. Herbal medicines are utilized extensively due to their





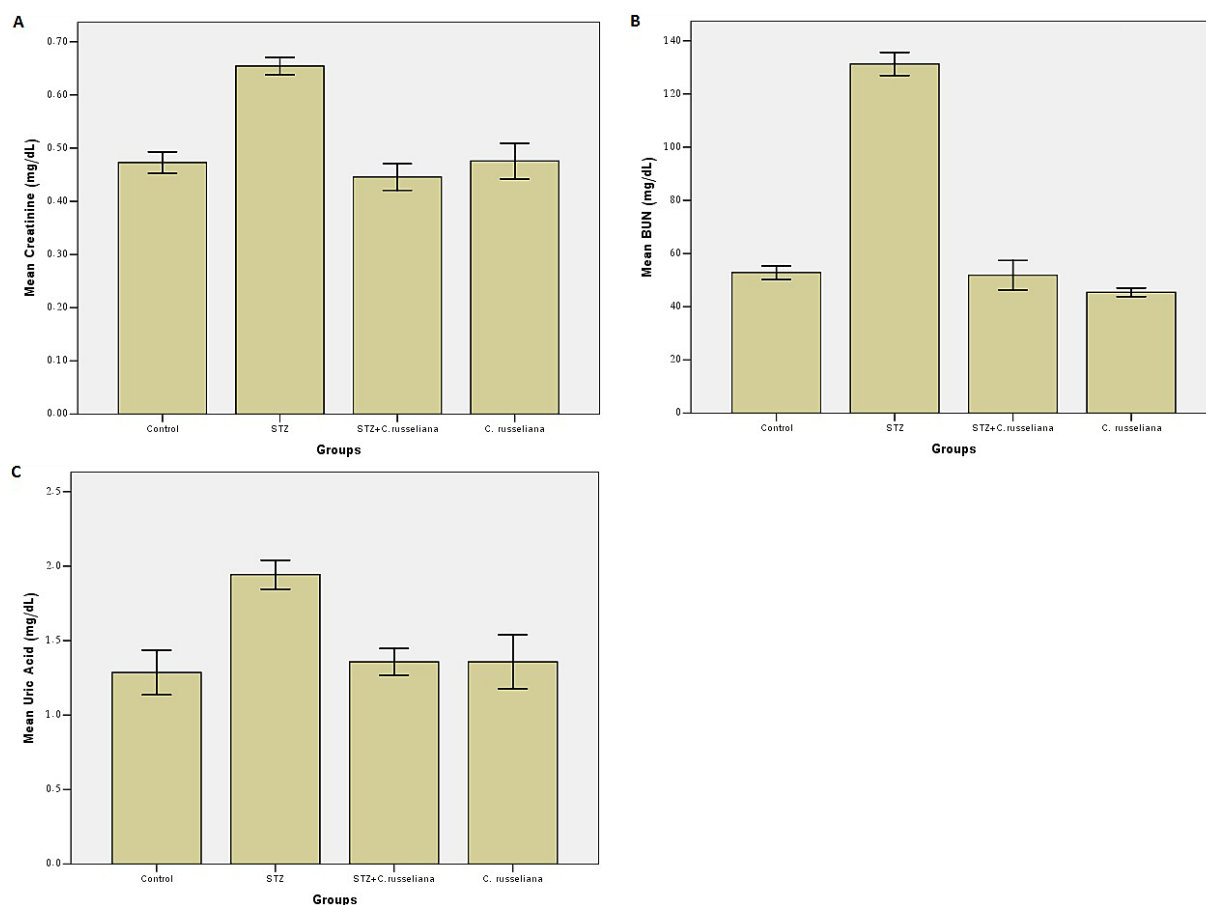
**Figure 4** Level of serum ALT (A), AST (B), ALP (C) and total bilirubin (D) in control, STZ, STZ plus *Caralluma russeliana* extract and *C. russeliana* extract-treated rats after 8 weeks. Error bars:  $\pm 1$  standard error of mean (n=7).

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; STZ, streptozotocin.

comparatively low costs and their much lower side effects. It has been demonstrated that many active ingredients derived from plants have an antidiabetic activity.<sup>34</sup> Leaves, stems, roots, barks, flowers, seeds and fruits may all be constituents of herbal medicines.<sup>35–40</sup> Several *Caralluma* species have been confirmed very efficient to treat DM such as *C. attenuata*,<sup>41</sup> *C. tuberculata*,<sup>42</sup> *C. sinaica* and *C. edulis* that can lead to a considerable decline in glucose concentrations.<sup>43</sup>

In this study, a significant decline in weight gain in STZ diabetic rats was noticed after 8 weeks. Similarly, these results are supported by several studies in STZ-diabetic animals.<sup>44–47</sup> The body weight reduction in diabetic animals may be due to protein loss as a result of lack of carbohydrates as a source of energy.<sup>48</sup> Increase in food consumption and reduction in body weight were observed in diabetic rats compared to normal rats, which reveals a polyphagic state and weight loss because of extreme destruction of tissue proteins.<sup>49</sup> Moreover, this study showed a considerable decline in weight gain in

non-diabetic rats treated with *C. russeliana* stem extract compared to normal control rats. *Caralluma* species such as *C. indica*, *C. attenuata*, *C. fimbriata* and *C. tuberculata* have anti-obesity activity.<sup>50</sup> *C. fimbriata* extract (100 mg/kg/day) has considerably decreased the increase in weight and lipid concentrations as compared to the control group fed on cafeteria diet. Therefore, this plant may be helpful in obesity treatment,<sup>51</sup> because it is able to reduce appetite and avoid fat deposition. It obstructs the creation of acetyl co-enzyme A and malonyl co-enzyme A, which are the basic components of fat synthesis.<sup>52</sup> The appetite suppressing action of *C. fimbriata* has been attributed to the active constituent pregnane glycosides. *C. fimbriata* might downregulate ghrelin creation in the stomach and neuropeptide-Y in the hypothalamus, leading to appetite suppression resulting in decreasing obesity.<sup>51</sup> Rising evidence implies that taking this plant for 60 days may reduce hunger, calorie intake and waistline.<sup>53</sup> Investigators compared baseline indicators of obesity such as serum



**Figure 5** Level of serum creatinine (A), BUN (B) and uric acid (C) in control, STZ, STZ plus *Caralluma russelliana* extract and *C. russelliana* extract-treated rats after 8 weeks. Error bars:  $\pm 1$  standard error of mean ( $n=7$ ).

**Abbreviations:** BUN, blood urea nitrogen; STZ, streptozotocin.

lipids, glucose, calorie intake, anthropometric measurements and appetite suppression with those after 60 days of taking of *C. fimbriata* extract.<sup>54</sup> The findings demonstrated decline in food consumption, body weight, body mass index, hip circumference and body fat. Comparable outcomes have been documented by Lawrence and Choudhary.<sup>55</sup> In another study, it is proved that *C. fimbriata* has not only the anti-obesogenic but also anti-atherosclerotic abilities.<sup>56</sup> In India, *Caralluma* species are edible and are used in the medicine. *C. fimbriata* in India is utilized to suppress appetite and to treat diabetes, pain, inflammation and fever. *C. tuberculata* is eaten and is generally utilized to treat diabetes, rheumatism, leprosy and as antipyretic.<sup>57,58</sup> *C. attenuata* is eaten raw to treat diabetes and its juice together with black pepper is used to treat migraine.<sup>59</sup> *C. adscendens* and *C. umbellata* have been documented for their antilipidemic activity. *C. fimbriata* has also revealed antiobesity activity.<sup>50</sup>

The present elevated levels of serum glucose, triglycerides, cholesterol, LDL-C and VLDL-C with the reduced levels of

total protein, albumin and HDL-C in group 2 diabetic rats reveal disturbances in carbohydrates, lipid and protein metabolism as a result of DM. Similar findings were observed by many experimental DM investigations.<sup>13,14,44,46,47,60,61</sup> Hypoproteinemia and hypoalbuminemia are linked with liver and kidney dysfunctions. Albumin is produced by the liver. It is a chief synthetic protein and is a marker of liver's capability to synthesize proteins.<sup>62</sup> Albumin is reliant on protein consumption and subject to feedback control by the plasma albumin concentration. Little albumin is filtered through the glomeruli and a large amount of that is reabsorbed by proximal tubule cells and degraded by their lysosomal enzymes into fragments returning to the circulation.<sup>63</sup> In DM, the level of circulating albumin is reduced. The degradation of albumin and relative volume of extravascular distribution in DM also decline by around 35%.<sup>64</sup>

DM and hyperlipidemia are two chief factors that intervene in the development of cardiovascular disease. Treatments of these situations are important modalities in heart disease prevention.<sup>65–67</sup> Faults in the action of insulin



and elevations in glucose may cause greater amounts of lipoproteins in the blood. Even little elevations in lipids in such diabetic patients are linked with a considerable rise in cardiovascular diseases.<sup>68</sup> The main plasma lipid constituents such as cholesterol and triglycerides do not circulate in the free state but are transported as complexes with lipoprotein. Any trouble in the metabolism of lipoprotein is revealed in the lipid profile and liver. As the liver has a main role in the metabolism of lipoprotein, any defect in its action results in lipid profile modifications. A number of factors might play a role in the accumulation of lipids in the liver. The accumulation of fat in the liver might take place if there is a disturbance in the production of lipoprotein, particularly its apoprotein division.<sup>69</sup> Increased levels of plasma HDL-C defend the arterial wall from the development of atherosclerotic plaque enhanced by reverse cholesterol transport.<sup>70</sup> Plasma HDL-C levels are changed by several means, including the absorption of complete HDL particle.<sup>71,72</sup> Several disturbances in metabolic and regulatory mechanisms, owing to insulin shortage, are accountable for the noted lipid accumulation.<sup>73</sup> Insulin secretion impairment leads to promoted lipid metabolism from the adipose tissue to the blood. In addition, it has been observed that diabetic rats treated with insulin demonstrate normalized lipid profile.<sup>74</sup> Furthermore, it is recognized that in uncontrolled diabetes, there will be elevation in cholesterol, triglycerides, LDL-C and VLDL-C with reduction in HDL-C, which leads to the coronary artery disease observed in some diabetic individuals.<sup>75,76</sup> Diabetes has odd lipid metabolism as insulin shortage in the body due to STZ caused harm to  $\beta$  cells in the pancreas. Insulin may trigger lipoprotein lipase, the enzyme lipoprotein solver. In DM, lipoprotein lipase activity reduced as a result of the elevation of concentrations of blood lipoproteins.<sup>77</sup>

In this study, serum cholesterol level was significantly reduced in non-diabetic rats treated with *C. russeliana* stem extract compared with other groups. These results revealed that *C. russeliana* stem extract may affect the metabolic processes of carbohydrates and lipids owing to their chemical constituents. Cholesterol-decreasing activity of *C. adscendens* aqueous extract showed hypolipidemic action.<sup>78</sup> Treatment with *C. fimbriata* aqueous extract at three different doses may considerably reduce total cholesterol and LDL cholesterol levels compared to controls. In addition, *C. umbellata* has revealed antilipidemic action, which may be owing to its active components.<sup>62</sup> Plant sterols (phytosterols) and plant stanols (phytostanols) are a vast group of compounds that are presented exclusively in plants. Williams and Gokool<sup>78</sup> reported that there are several methods in which

plant sterols and stanols stop absorption and, therefore, lower cholesterol. Thus, cholesterol is excreted through feces.

This study demonstrated that STZ induced an increase in serum ALT, AST, ALP and total bilirubin levels in rats, because necrosis or damage to the membrane discharges them into circulation, which is consistent with the formerly reported results.<sup>80</sup> Serum concentrations of these compounds are very liable markers in liver disease diagnosis.<sup>81</sup> Diabetic persons have elevated liver function test abnormalities than non-diabetic patients.<sup>82,83</sup> The high levels of these parameters were pinpointing cellular leakage and functional integrity loss of the cell membranes.<sup>84</sup> *C. diazielli* extract has significantly decreased serum liver enzyme levels (AST, alanine transaminase, ALP) in rats with fructose-induced diabetes.<sup>85</sup>

This study examined the kidney function by measuring serum creatinine, BUN and uric acid concentrations. The current increase in these biochemical parameters proved renal dysfunction in untreated diabetic rats. Creatinine, BUN and uric acid are protein metabolism waste products that require to be excreted through the kidney, consequently an obvious elevation of these compounds, as noticed in this study, validates a signal of kidney functional damage.<sup>86</sup> Hyperglycemia excites oxidative abuse in renal tubular epithelial cells and that damage starts tubulointerstitial fibrosis, a distinctive characteristic of diabetic nephropathy, which then progressively leads to renal failure.<sup>87,88</sup> It is reported that nephropathy develops in 30%–40% of the diabetic patients and has globally become an important reason of end-stage renal failure.<sup>89,90</sup> Diabetic nephropathy is distinguished by structural and functional abnormalities.<sup>91</sup> Defective glycemic control and accumulation of advanced glycation end products (AGEs) play a major role in diabetic nephropathy development.<sup>90</sup> Furthermore, Mestry et al<sup>91</sup> showed that untreated STZ-diabetic rats exhibit a marked damage in renal function, which is proved by the increase in serum creatinine, BUN and uric acid levels.

A number of *Caralluma* species demonstrated antihyperglycemic action of their extracts or fractions.<sup>93</sup> Abdel-Sattar et al<sup>92</sup> evaluated the antihyperglycemic effects of *C. quadrangula* indigenous to Saudi Arabia on STZ-induced diabetic rats. The outcomes revealed a considerable decline in the levels of blood glucose in diabetic-treated rats after the treatment of most extracts and fractions of *C. quadrangula* and glibenclamide. They concluded that their study confirmed the traditional use of this species to treat DM. Its extract has been utilized in Saudi traditional medicine for the treatment of diabetes, melasma, freckles, vitiligo and in cases of thirst and hunger.

In this study, treatments with *C. russeliana* stem extract in diabetic rats revealed significant declining and defending

effects of physiological modifications. The medicinal values of *Caralluma* depend on their phytochemical constituents that generate beneficial physiological activities. In *Caralluma*, the main and distinctive phytochemical components are pregnane glycosides, flavone glycosides, megastigmane glycosides, triterpenes, bitter principles and saponins.<sup>29,30</sup>

The aerial parts of *C. russeliana* from Saudi Arabia contain several phytochemical compounds such as acylated pregnane glycosides, russeliosides A–D (1–4), flavone glycoside, luteolin 4'-O- $\beta$ -D-neohesperidoside, russeliosides, 14 $\beta$ -benzoyloxy-15 $\beta$ -isovaleroyloxy-16 $\beta$ -hydroxypregn-20-on-3-O-( $\beta$ -D-3-O-methyl-6-deoxyoleandrosopyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-cymaropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-cymaropyranoside) (1) and 14 $\beta$ -isovaleroyloxy-15 $\beta$ -benzoyloxy-16 $\beta$ -hydroxypregn-20-on-3-O-( $\beta$ -D-3-O-methyl-6-deoxyoleandrosopyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-cymaropyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-cymaropyranoside) (2).<sup>25,31,94,95</sup> A number of *Caralluma* species have been utilized to treat different diseases, such as rheumatism, diabetes, cancer, tuberculosis, leprosy, scabies, fever, inflammation, snake and scorpion bites, as antiseptic and disinfectant.<sup>96</sup>

*C. sinica* administration in varied doses to healthy animals can cause a considerable decline in the level of glucose.<sup>97</sup> *C. attenuata* and *C. edulis* extracts had hypoglycemic activities and provide synergistic influence in combination with phlorizin extract that usefully alters the levels of blood insulin, blood and urine glucose as well as glucose transport and aids in weight loss.<sup>98</sup> Abdel-Sattar et al<sup>99</sup> studied the potential and mechanisms of the antidiabetic activity of different *C. tuberculata* extracts in STZ-induced diabetic rats. Both methanolic extract and the remaining water fractions demonstrated the highest strength, where methanolic extract had greater activity. The main mechanism for the noticed antihyperglycemic activity of methanolic extract might be credited to improved skeletal muscle use of glucose, hepatic gluconeogenesis inhibition and insulin secretion stimulation.<sup>99</sup> Latha et al<sup>100</sup> demonstrated that oral administration of *C. fimbriata* methanol extract to STZ-induced diabetic rats at a dose of 100 and 200 mg/kg body weight caused a considerable decrease in blood glucose at varied treatment periods. The methanol extract-treated diabetic rats were notably improved from diabetic and renal toxicity as well as hepatotoxicity, by analyzing certain factors such as glycosylated hemoglobin, plasma insulin, body weight, total protein, ALP, serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase. Moreover, the histopathological outcome of methanol extract-treated rats proved the noteworthy recovery of liver and kidney damage. They concluded that the study revealed the therapeutic influence

of methanol extract for DM and its associated complications. Poodineh and Nakhaee<sup>101</sup> evaluated the antidiabetic influences of two doses of *C. tuberculata* suspension and its safety on STZ-induced diabetic rats. *C. tuberculata*-treated groups displayed a considerable improvement in aberrations of oral glucose tolerance test, hematological and biochemical parameters compared to the diabetic control group. In addition, *C. tuberculata* at both doses (100 and 200 mg/kg) revisited considerably DM-induced modifications in lipid profile excluding the level of HDL-C that was notably elevated at a dose of 200 mg/kg. No significant variation was found in hematological, kidney and liver parameters between normal control and normal rats getting *C. tuberculata*. Therefore, the authors concluded that this plant might be useful for improving hyperlipidemia, hyperglycemia and hematological alterations excited by DM. Furthermore, it could guard the kidney and liver against complications as a result of DM without any poisonous effects.

## Conclusion

The data of this study demonstrated a significant effect of *C. russeliana* stem extract on certain physiological parameters in STZ-induced diabetes in male rats after 8 weeks. The lowest body weight gain was noticed in diabetic rats of group 2. Serum glucose, triglycerides, cholesterol, LDL-C, VLDL-C, ALT, AST, ALP, total bilirubin, creatinine, BUN and uric acid levels were significantly elevated in diabetic rats of group 2; however, serum total protein, albumin and HDL-C levels were significantly reduced. Treatments with *C. russeliana* stem extract in diabetic rats revealed notable decreasing and protecting effects of physiological modifications. Therefore, this study revealed the significance of using *C. russeliana* stem extract as a potential therapeutic agent to treat DM and its complications. Finally, further research is needed to establish the efficacy of various extracts of this plant and their constituents to treat DM and to clarify their action mechanisms on diabetic models.

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## Author contributions

TZ and MA-T contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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